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(57) Abstract

Controlled release dosage forms useful in the treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease.

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COMPOSITION

The present invention relates to novel formulations, and to their use in the treatment and/or prophylaxis of certain disorders.

[R-(Z)]-α-(methoxyimino)-α-(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) and methods for its preparation are disclosed in EP-A-0392803, WO95/31456 and WO93/17018. The compound enhances acetylcholine function via an action at muscarinic receptors within the central nervous system, and is therefore of potential use in the treatment and/or prophylaxis of dementia in mammals.

WO96/12486 discloses the use of compound X in the manufacture of a medicament for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease.

Fast-release swallow tablet and oral solution formulations of compound X both result in rapid absorption of the compound into the circulation, and require twice a day dosing for optimal efficacy.

It has now been surprisingly found that it is possible to formulate compound X, which has very high water solubility and is active at extremely low doses, in such a way that release is controlled to take place over a period of hours. Such a formulation would require dosing only once a day: this is likely to improve compliance in a patient population characterised by poor memory; it may also reduce side-effects in case of accidental overdosing.

Accordingly, in a first aspect the present invention provides a controlled release oral dosage form containing 0.04 %w/w pfb compound X and 98.5-99.5%w/w total mono, di and triglycerides and polyethylene glycol mono and diesters consisting of Gelucire 50/13 (EP) and Gelucire 50/02 (Fr Ph) in a ratio of >0.02 Gelucire 50/13 (EP) to Gelucire 50/02 (Fr Ph), in a hard gelatin capsule containing 0.10 mg/capsule compound X pfb, such that the release profile of the capsule in 1mM HCl is 20-60% after 8hr.

Preferably the release profile after 8hr is 20-40% or 30-60%.

Gelucire 50/13 (EP) is a mixture of mono, di and triglycerides and polyethylene glycol mono and diesters specified in the European Pharmacopeia "Stearoyl Macroglycerides" (Supplement 1998) as:

specific mixtures of monoesters, diesters and triesters of glycerol and monoesters and diesters of macrogols with a mean relative molecular mass between 300 and 4000 comprising:

free glycerol content: < 3%
lauric acid (C12): < 5%
myristic acid (C14): < 5%
different nominal amounts of stearic acid (C18) and of palmitic acid (C16).

The sum of stearic acid and of palmitic acid is not less than 90%.

Gelucire 50/02 (Fr Ph) is a mixture of mono, di and triglycerides and polyethylene glycol mono and diesters specified in the French Pharmacopoeia "Glycerides Polyglycolyses Satures" (1990) as:
specific mixtures of mono, di and triglycerides and polyethylene glycol mono and diesters, obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging 200-2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging 200 -2000, comprising:

free glycerol content: < 3%
caprylic acid (C8): < 15%
capric acid (C10): < 15%
lauric acid (C12): < 50%
myristic acid (C14): < 25%
palmitic acid (C16): < 55%
stearic acid (C18): < 97%

The mono, di and triglycerides and polyethylene glycol mono and diesters preferably make up 99.41% of the dosage form. The ratio of Gelucire 50/13 (EP) to Gelucire 50/02 (Fr Ph) is preferably <0.055, more preferably ≤0.053.

In a preferred aspect the mixture of mono, di and triglycerides and polyethylene glycol mono and diesters consists of Gelucire 50/13 (Gattefosse) and Gelucire 50/02 (Gattefosse). Most preferably the composition comprises 97.41% Gelucire 50/13 (Gattefosse) and 2.00% Gelucire 50/02 (Gattefosse) or 94.41% Gelucire 50/13 (Gattefosse) and 5.00% Gelucire 50/02 (Gattefosse).

The composition preferably additionally comprises propylene glycol, preferably at 0.45% w/w (1.13mg/capsule).

The composition preferably additionally comprises 3,4,5-trihydroxybenzoic acid propyl ester, preferably at 0.10% w/w (0.25mg/capsule).

In a preferred embodiment of the first aspect the composition is selected from:

Component	% w/w	mg/capsule
Compound X	0.04 pfb	0.10 pfb
Gelucire 50/02 (EP)	94.41	236.00
Gelucire 50/13 (Fr Ph)	5.00	12.50
propylene glycol	0.45	1.13
3,4,5-trihydroxybenzoic acid propyl ester	0.10	0.25

and

Component	% w/w	mg/capsule
Compound X	0.04 pfb	0.10 pfb
Gelucire 50/02 (EP)	97.41	243.52
Gelucire 50/13 (Fr Ph)	2.00	5.00
propylene glycol	0.45	1.13
3,4,5-trihydroxybenzoic acid propyl ester	0.10	0.25

in a hard gelatin capsule.

In a second aspect, the present invention provides a controlled release oral dosage form containing compound X of the following composition:

Ingredient	mg/tablet	%/tablet
Compound X	0.005-0.1pfb	
hydroxpropyl methylcellulose	37.5 - 45	25 - 30
dibasic calcium phosphate dihydrate	45 - 52.5	30 - 35
microcrystalline cellulose (nominal mean particle size 50 microns)	19.5	13.0
microcrystalline cellulose (nominal mean particle size 100 microns)	37.76	25.2

granulated, compressed into tablets and coated to a 3% weight gain with a seal coat consisting of a solution of hydroxypropyl methylcellulose aqueous dispersion with plasticizer in purified water at 10% solids followed by a coat consisting of

ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polytheylene glycol plasticizer, such that 40-65% of the drug is released within 8 hours in water.

The composition preferably additionally comprises:
sodium dihydrogen citrate, preferably at a level of 1.50mg/tablet (1.0%) and/or magnesium stearate, preferably at a level of 1.125mg/tablet (0.75%).

In preferred embodiments of the second aspect:

hydroxpropyl methylcellulose is Methocel E4M CR;

microcrystalline cellulose (nominal mean particle size 50 microns) is Avicel PH101;

microcrystalline cellulose (nominal mean particle size 100 microns) is Avicel PH102;

hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and is preferably Opadry White or Opadry Clear (YS-1-9025A); and/or

ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer and is preferably Surelease Clear (E-7-19010).

In a third aspect, the present invention provides a controlled release oral dosage form containing compound X of the following composition:

Ingredient	**mg/tablet**	**%/tablet**
Compound X	0.005-0.1pfb	
ethylcellulose	22.5 - 37.5	15 - 25
dibasic calcium phosphate dihydrate	63.3 - 78.3	42.2-52.2
microcrystalline cellulose	30.0-40.0	19.8-26.7

compressed into tablets and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and and hydroxypropylmethylcellulose aqueous dispersion with plasticizer.

In one preferred embodiment of the third aspect the composition additionally comprises sodium dihydrogen citrate, preferably at a level of 3.00mg/tablet (2.0%) and/or colloidal silicon dioxide, preferably at a level of 0.75mg/tablet (0.50%)

and/or magnesium stearate, preferably at a level of 1.125mg/tablet (0.75%) and/or the microcrystalline cellulose has a mean particle size of 100 microns, preferably at a level of 32.5mg/tablet (21.7%); and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polytheylene glycol plasticizer, such that 35 - 50 % of the drug is released within 8 hours in water.

In a second preferred embodiment of the third aspect the composition is wet granulated before compression using an ethyl cellulose aqueous dispersion containing oleic acid, ammonium hydroxide and plasticizer, preferably at a level of 7.5-15.0mg/tablet (5.0 - 10.0%). Where the composition is wet granulated, it additionally comprises sodium dihydrogen citrate, preferably at a level of 1.50mg/tablet (1.0%), and/or magnesium stearate, preferably at a level of 1.125mg/tablet (0.75%), and/or the micorcrystalline cellulose has a mean particle size of 50 microns, preferably at a level of 37.5mg/tablet (25%); and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with plasticizer such that 60-75% of the drug is released within 8 hours in water.

In preferred embodiments of the third aspect:

ethylcellulose is Ethocel Std 7;

microcrystalline cellulose (nominal mean particle size 50 microns) is Avicel PH101;

microcrystalline cellulose (nominal mean particle size 100 microns) is Avicel PH102;

hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and is preferably Opadry Clear (YS-1-9025A); and/or

ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer and is preferably Surelease Clear (E-7-19010).

By controlled release is meant release of the active substance from the dosage form is modified to occur at a slower rate than that from an immediate release product, such as a conventional swallow tablet or capsule.

The dosage form of the invention may be used in the treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease. These disorders are herein after referred to as "the Disorders".

The present invention provides a method of treating "the Disorders" by administering an effective amount of the controlled release oral dosage form of the invention to a sufferer in need thereof.

The present invention further provides the use of a controlled release oral dosage form of the invention in the manufacture of a medicament for treating "the Disorders".

The present invention also provides a pharmaceutical composition for use in the treatment of "the Disorders" which comprises a controlled release oral dosage form of the invention.

The following example illustrates the present invention. The weight shown is the weight of free base (pfb = pure free base). Mesh sizes are US standard.

Example 1

Component	**% w/w**	**mg/capsule**	**Function**
Compound X	0.04 pfb	0.10 pfb	Active
Gelucire 50/02*	94.41	236.00	Wax matrix
Gelucire 50/13*	5.00	12.50	Wax matrix
propylene glycol	0.45	1.13	Solvent
propyl gallate**	0.10	0.25	Antioxidant

Example 2

Component	**% w/w**	**mg/capsule**	**Function**
Compound X	0.04 pfb	0.10 pfb	Active
Gelucire 50/02*	97.41	243.52	Wax matrix
Gelucire 50/13*	2.00	5.00	Wax matrix
propylene glycol	0.45	1.13	Solvent
propyl gallate**	0.10	0.25	Antioxidant

*specific mixture of mono, di and triglycerides, and polyethylene glycol mono and diesters of the following compositions:

Gelucire 50/13 (Gattefosse, certificate of analysis):

Free glycerol content: < 3%
Caprylic acid: < 3%
Capric acid: < 3%
Lauric acid: < 5%
Myristic acid: < 5%
Palmitic acid: 40-50%
Stearic acid: 48-58%

Gelucire 50/02 (Gattefosse, certificate of analysis):

Free glycerol content: < 3%
Caprylic acid: < 3%
Capric acid: < 3%
Lauric acid: 4-14%
Myristic acid: 2-12%
Palmitic acid: 32-42%
Stearic acid: 37-47%

**3,4,5-trihydroxybenzoic acid propyl ester

Process for Examples 1 and 2:

Waxes were melted together at around 60 degrees C and mixed with propyl gallate. Compound X was dissolved in propylene glycol, and blended into the waxes. The mixture was filled into size 3 hard gelatin capsule shells.

Release profiles

Dissolution equipment conforming to an apparatus No.2 of USP.
Medium: 1 mM HCl.
Volume: 500 mL
Temperature: 37C.
Paddle speed: 50rpm.

Table 1.: Release Profile of wax-filled capsules of Example 1

Time (hr)	% Released
2	17
4	27
8	46
15	70
23	86

Table 2.: Release Profile of wax-filled capsules of Example 2

Time (hr)	% Released
2	10
4	18
8	29
15	44
23	56

Example 3

Ingredient	**mg/tablet**	**Function**
Compound X	0.005-0.1pfb	Active
Methocel E4M CR	37.5	Hydrogel matrix
sodium dihydrogen citrate	1.50	Stabilizer
dibasic calcium phosphate dihydrate	52.5	Hydrophobic diluent
Avicel PH101	19.5	Hydrophobic diluent
Avicel PH102	37.76	Hydrophobic diluent
magnesium stearate	1.125	Lubricant
purified water	q.s.	

Tablets were prepared by the following procedure:

1. Preblend the drug with a small quantity of the excipients
2. Wet granulate using high shear granulation
3. Dry granulation using fluid bed or oven process
4. Screen through a comminuting mill
5. Blend the remaining excipients with the drug granluation
6. Lubricate with magnesium stearate

7. Compress into tablets
8. Coat tablets with polymer

Seal coating solution:

A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations was made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

Polymer Coating:

A polymer coating dispersion containing ethylcellulose (Surelease Clear (E-7-19010)) and Opadry Clear (YS-1-9025A) of the following composition was made and used for polymer coating the seal coated beads at 4-5% weight gain.

Component	% w/w	Function
Surelease Clear (E-7-19010)	4.5 (25% as solids)	Release controlling polymer coat with plasticiser
Opadry Clear(YS-1-9025A)	0.5	Release controlling polymer coat
Purified water	q.s.	
Total	100	

700 grams of core tablets were coated using a Vector LDCS pan to a 3% weight gain with the Opadry Clear (YS-1-9025A) seal coating solution. The seal coated tablets were then polymer coated to 4-5% weight gain using the Surelease/Opadry coating dispersion.

Table 3. Release Profile for tablet of Example 3 of Compound X in water

Time (hr)	% Dissolved	
	4% coat	5% coat
1	0.14	0.17
2	0.61	0.35
4	19.9	6.6
8	62	52
12	87	92

Example 4

Ingredient	mg/tablet	Function
Compound X	0.005-0.1pfb	Active
Ethocel Std 7	30.0	Hydrogel matrix
sodium dihydrogen citrate	1.50	Stabilizer
dibasic calcium phosphate dihydrate	70.76	Hydrophobic diluent
Avicel PH101	37.5	Hydrophobic diluent
Surelease Clear (E-7-19010)	9.0	Hydrogel matrix
magnesium stearate	1.125	Lubricant

Tablets were prepared by the following procedure:

1. Preblend the drug with a small quantity of the excipients
2. Granulate mix with Surelease dispersion using high shear granulation and wet screen resulting granulation
3. Dry granulation using fluid bed
4. Screen through a sizing mill
5. Blend the remaining excipients with the drug granluation
6. Lubricate with magnesium stearate
7. Compress into tablets
8. Coat tablets with polymer

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations was made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

Polymer Coating: A polymer coating dispersion containing ethylcellulose (Surelease (E-7-19010) and Opadry Clear (YS-1-9025A) of the following composition was made and used for polymer coating the seal coated tablets at 4-5% weight gain.

Component	% w/w	Function
Surelease Clear (E-7-19010)	4.25 (25% as solids)	Release controlling polymer coat with plasticiser
Opadry Clear (YS-1-9025A)	0.75	Release controlling polymer coat
purified water	q.s.	
Total	100	

700 grams of core tablets were coated using a Vector LDCS pan to a 3% weight gain with the Opadry Clear seal coating solution. The seal coated tablets were then polymer coated to 4-5% weight gain using the Surelease/Opadry coating dispersion.

Table 4. Release Profile for the tablet of Example 4 of Compound X in water

Time (hr)	% Dissolved	
	4% coat	5% coat
1	2.1	0.57
2	7.4	3.1
4	35	26
8	73	71
12	90	88

Example 5

Ingredient	**mg/tablet**	**Function**
Compound X	0.005-0.1pfb	Active
Ethocel Std 7	37.5	Hydrogel matrix
sodium dihydrogen citrate	3.00	Stabilizer
dibasic calcium phosphate dihydrate	75.0	Hydrophobic diluent
Avicel PH102	32.5	Hydrophobic diluent
colloidal silicon dioxide	0.75	Glidant
magnesium stearate	1.125	Lubicant

Tablets were prepared by the following procedure:

1. Preblend the drug with a small quantity of the excipients
2. Blend the remaining excipients with the drug preblend
3. Lubricate with magnesium stearate
4. Compress into tablets
5. Coat tablets with polymer

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations was made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

Polymer Coating: A polymer coating dispersion containing ethylcellulose (Surelease (E-7-19010)) and Opadry Clear (YS-1-9025A) of the following

composition was made and used for polymer coating the seal coated tablets at 4% weight gain.

Component	% w/w	Function
Surelease Clear (E-7-19010)	3.4 (25% as solids)	Release controlling polymer coat with plasticiser
Opadry Clear (YS-1-9025A)	0.6	Release controlling polymer coat
purified water	q.s.	
Total	100	

700 grams of core tablets were coated using a Vector LDCS pan to a 3% weight gain with the Opadry Clear seal coating solution. The seal coated tablets were then polymer coated to 4% weight gain using the Surelease/Opadry coating dispersion.

Table 5. Release Profile for tablet of Example 5 of Compound X in water

Time (hr)	% Dissolved
2	6.2
4	14
8	38
12	66
16	90

Tradename	Generic description	Supplier
Ethocel Std 7	ethylcellulose (viscosity 5%w/v solution of 6.4 mPa mean particle size 210microns)	Dow
Methocel E4M CR	hydroxpropyl methcellulose (nominal viscosity, 2% in water, of 4000) %methoxyl=28-30, 95%<100 mesh)	Dow
Avicel PH101	microcrystalline cellulose (nominal mean particle size 50 microns)	FMC Corp
Avicel PH102	microcrystalline cellulose (nominal mean particle size 100 microns)	FMC Corp
Opadry Clear (YS-1-9025A)	hydroxymethylcellulose aqueous dispersion with polyethylene glycol plasticizer	Colorcon
Surelease Clear (E-7-19010)	aqueous dispersion of ethyl cellulose, oleic acid, ammonium hydroxide, fractionated coconut oil plasticizer	Colorcon

CLAIMS

1. A controlled release oral dosage form containing [R-(Z)]-α-(methoxyimino)-α-(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) of the following composition:

Ingredient	**mg/tablet**	**%/tablet**
Compound X	0.005-0.1pfb	
ethylcellulose	22.5 - 37.5	15 - 25
dibasic calcium phosphate dihydrate	63.3 - 78.3	42.2-52.2
microcrystalline cellulose	30.0-40.0	19.8-26.7

compressed into tablets and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and and hydroxypropylmethylcellulose aqueous dispersion with plasticizer.

2. A dosage form according to claim 1 which additionally comprises sodium dihydrogen citrate and/or colloidal silicon dioxide and/or magnesium stearate and/or the microcrystalline cellulose has a mean particle size of 100 microns; and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polytheylene glycol plasticizer, such that 35 - 50 % of the drug is released within 8 hours in water.

3. A dosage form according to claim 2 which comprises sodium dihydrogen citrate at a level of 3.00mg/tablet (2.0%) and/or colloidal silicon dioxide at a level of 0.75mg/tablet (0.50%) and/or magnesium stearate at a level of 1.125mg/tablet (0.75%) and/or microcrystalline cellulose at a level of 32.5mg/tablet (21.7%).

4. A dosage form according to claim 1 wherein the composition is wet granulated before compression using an ethyl cellulose aqueous dispersion containing oleic acid, ammonium hydroxide and plasticizer.

5. A dosage form according to claim 4 wherein the ethyl cellulose dispersion is at a level of 7.5-15.0mg/tablet (5.0 - 10.0%).

6. A dosage form according to claim 4 or 5 which additionally comprises sodium dihydrogen citrate and/or magnesium stearate and/or the micorcrystalline

cellulose has a mean particle size of 50 microns; and coated to a 3% weight gain with a seal coating solution consisting of hydroxymethylcellulose aqueous dispersion with plasticizer in purified water at 10% solids concentration followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with plasticizer such that 60-75% of the drug is released within 8 hours in water.

7. A dosage form according to claim 6 which comprises sodium dihydrogen citrate at a level of 1.50mg/tablet (1.0%) and/or magnesium stearate at a level of 1.125mg/tablet (0.75%) and/or micorcrystalline cellulose at a level of 37.5mg/tablet (25%).

8. A dosage form according to any one of claims 1 to 7 wherein the hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and/or the ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer.

9. A controlled release oral dosage form according to claim 1 of the following composition:

Ingredient	**mg/tablet**
Compound X	0.005-0.1pfb
Ethocel Std 7	30.0
sodium dihydrogen citrate	1.50
dibasic calcium phosphate dihydrate	70.76
Avicel PH101	37.5
Surelease Clear (E-7-19010)	9.0
magnesium stearate	1.125

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations made by dissolving 100 grams of Opadry Clear into 900 grams of purified water (to 3% weight gain);

Polymer Coating: (4-5% weight gain)

Component	**% w/w**
Surelease Clear (E-7-19010)	4.25 (25% as solids)
Opadry Clear (YS-1-9025A)	0.75
purified water	q.s.
Total	100.

10. A controlled release oral dosage form according to claim 1 of the following composition:

Ingredient	**mg/tablet**	**Function**
Compound X	0.005-0.1pfb	Active
Ethocel Std 7	37.5	Hydrogel matrix
sodium dihydrogen citrate	3.00	Stabilizer
dibasic calcium phosphate dihydrate	75.0	Hydrophobic diluent
Avicel PH102	32.5	Hydrophobic diluent
colloidal silicon dioxide	0.75	Glidant
magnesium stearate	1.125	Lubicant

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations made by dissolving 100 grams of Opadry Clear into 900 grams of purified water (to 3% weight gain);

Polymer Coating: (4% weight gain):

Component	**% w/w**
Surelease Clear (E-7-19010)	3.4 (25% as solids)
Opadry Clear (YS-1-9025A)	0.6
purified water	q.s.
Total	100.

11. A controlled release oral dosage form containing [R-(Z)]-α-(methoxyimino)-α-(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) of the following composition:

Ingredient	**mg/tablet**	**%/tablet**
Compound X	0.005-0.1pfb	
hydroxpropyl methylcellulose	37.5 - 45	25 - 30
dibasic calcium phosphate dihydrate	45 - 52.5	30 - 35
microcrystalline cellulose (nominal mean particle size 50 microns)	19.5	13.0
microcrystalline cellulose (nominal mean particle size 100 microns)	37.76	25.2

granulated, compressed into tablets and coated to a 3% weight gain with a seal coat consisting of a solution of hydroxypropyl methylcellulose aqueous dispersion with

plasticizer in purified water at 10% solids followed by a coat consisting of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer or a mixture of ethylcellulose aqueous dispersion with oleic acid, ammonium hydroxide and plasticizer and hydroxypropylmethylcellulose aqueous dispersion with polytheylene glycol plasticizer, such that 40-65% of the drug is released within 8 hours in water.

12. A dosage form according to claim 11 which additionally comprises: sodium dihydrogen citrate and/or magnesium stearate.

13. A dosage form according to claim 12 which comprises sodium dihydrogen citrate at a level of 1.50mg/tablet (1.0%) and/or magnesium stearate at a level of 1.125mg/tablet (0.75%)

14. A dosage form according to any one of claims 11 to 13 wherein the hydroxypropyl methylcellulose aqueous dispersion has polyethylene glycol plasticizer and/or the ethylcellulose aqueous dispersion has fractionated coconut oil plasticizer.

15. A controlled release oral dosage form according to claim 11 of the following composition:

Ingredient	**mg/tablet**
Compound X	0.005-0.1pfb
Methocel E4M CR	37.5
sodium dihydrogen citrate	1.50
dibasic calcium phosphate dihydrate	52.5
Avicel PH101	19.5
Avicel PH102	37.76
magnesium stearate	1.125
purified water	q.s.

Seal coating solution: A solution of Opadry Clear (YS-1-9025A) in purified water at 10% solids concentrations made by dissolving 100 grams of Opadry Clear into 900 grams of purified water.

Polymer Coating (4-5% weight gain):

Component	**% w/w**
Surelease Clear (E-7-19010)	4.5 (25% as solids)
Opadry Clear(YS-1-9025A)	0.5
Purified water	q.s.
Total	100

16. A controlled release oral dosage form containing 0.04 %w/w pfb [R-(Z)]-α-(methoxyimino)-α-(1-azabicyclo [2.2.2]oct-3-yl)acetonitrile monohydrochloride (compound X) and 98.5-99.5%w/w total mono, di and triglycerides and polyethylene glycol mono and diesters consisting of Gelucire 50/13 (EP) and Gelucire 50/02 (Fr Ph) in a ratio of >0.02 Gelucire 50/13 (EP) to Gelucire 50/02 (Fr Ph), in a hard gelatin capsule containing 0.10 mg/capsule compound X pfb, such that the release profile of the capsule in 1mM HCl is 20-60% after 8hr.

17. A dosage form according to claim 16 wherein the release profile after 8hr is 20-40% or 30-60%.

18. A dosage form according to claim 16 or 17 which comprises 97.41% Gelucire 50/13 and 2.00% Gelucire 50/02 or 94.41% Gelucire 50/13 and 5.00% Gelucire 50/02.

19. A dosage form according to any of claims 16 to 18 which additionally comprises propylene glycol.

20. A dosage form according to claim 19 which comprises propylene glycol at 0.45% w/w.

21. A dosage form according to any of claims 16 to 20 which additionally comprises 3,4,5-trihydroxybenzoic acid propyl ester.

22. A dosage form according to claim 21 which comprises 3,4,5-trihydroxybenzoic acid propyl ester at 0.10% w/w.

23. A dosage form according to any of claims 16 to 22 which comprises 0.04% pfb w/w compound X.

24. A dosage form according to claim 16 selected from:

Component	**% w/w**	**mg/capsule**
Compound X	0.04 pfb	0.10 pfb
Gelucire 50/02 (EP)	94.41	236.00
Gelucire 50/13 (Fr Ph)	5.00	12.50
propylene glycol	0.45	1.13
3,4,5-trihydroxybenzoic acid propyl ester	0.10	0.25

and

Component	% w/w	mg/capsule
Compound X	0.04 pfb	0.10 pfb
Gelucire 50/02 (EP)	97.41	243.52
Gelucire 50/13 (Fr Ph)	2.00	5.00
propylene glycol	0.45	1.13
3,4,5-trihydroxybenzoic acid propyl ester	0.10	0.25

in a hard gelatin capsule.

25. A process for preparing a dosage form as defined in any one of claims 1 to 24 which process comprises admixing the ingredients.

26. A method of treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease by administering an effective amount of the dosage form of any one of claims 1 to 24 to a sufferer in need thereof.

27. The use of a dosage form of any one of claims 1 to 24 in the manufacture of a medicament for treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease.

28. A pharmaceutical composition for use in the treatment and/or prophylaxis of dementia, including Alzheimer's disease, in mammals, and/or for enhancing amyloid precursor protein processing along a non-amyloidogenic pathway in patients suffering from, or at risk of developing, Alzheimer's disease which comprises a dosage form of any one of claims 1 to 24.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/435 A61K9/48 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,A	WO 98 10762 A (NAPPER JAMES ALBERT ;ROUSSEAU LAURENCE (GB); SMITHKLINE BEECHAM PL) 19 March 1998 (1998-03-19) the whole document -----	1-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 1999	26/08/1999

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1

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